

RESEARCH ARTICLE

Vaginal Dose, Toxicity and Sexual Outcomes in Patients of Cervical Cancer Undergoing Image Based Brachytherapy

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Abstract

Background: The aim of the study was to evaluate the vaginal dose and toxicity in patients of cervical cancer treated with image guided brachytherapy at our institute. **Materials and Methods:** Thirty-five patients treated with image based brachytherapy for cervical cancer were included. Vaginal contouring was done on MRI at brachytherapy and with CT scans of subsequent brachytherapy fractions. Dose volume parameters (DVH) were reported in accordance with the GEC-ESTRO guidelines. These were correlated with vaginal toxicity (assessed by CTC AE version 3) and quality of sexual life assessed at one year of completion of treatment. **Results:** Vaginal shortness was observed in 22 out of 30 (62.8%) patients, Nine (25.7%) had vaginal dryness and in 10 (28.5%) patients, there was contact bleeding. No association could be demonstrated between the dose volume parameters and vaginal toxicity in the present study. **Conclusions:** The lack of association between dose volume parameters of vagina with vaginal morbidity may be due to uncertainties involved in the delineation of vaginal wall and dosimetry. Future research is required to accurately define vaginal dose distribution to study its correlation with vaginal morbidity. Vaginal morbidity needs to be documented in order to improve the sexual outcome in these patients.

Keywords: Radiation - vagina - toxicity - dose volume parameters - sexual outcome

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Introduction

The standard treatment for locally advanced cancer cervix consists of external beam radiotherapy with concurrent cisplatin and intracavitary brachytherapy. With three-dimensional (3-D) planning techniques using computed tomography (CT) and Magnetic resonance imaging (MRI), improved tumor doses with effective sparing of organs at risk is now possible. With improvement in the treatment outcomes and increase in the longevity of patients, concerns over quality of life are of utmost importance. In brachytherapy of cancer cervix, dose escalation with the use of MRI based image-guided brachytherapy has shown an improvement in the local control rates (Potter et al., 2011). With image-based brachytherapy the organ walls can be contoured and the dose reporting to individual organs can be done using the dose volume parameters (DVH) introduced by the Gynecological (GYN) European Society for Radiotherapy and Oncology (GEC-ESTRO) (Potter et al., 2006). Whereas reporting of doses and dose constraints to the bladder, rectum and sigmoid have been suggested by the GEC-ESTRO, the assessment of vaginal doses is difficult due to the steep dose gradient and high uncertainties due to

the close proximity of vagina to the high dose regions (Potter et al., 2006). In addition, inaccuracies in contouring with significant inter and intra observer variations may result in large dose variations (Berger et al., 2007). Traditionally vagina has been considered a relatively radio resistant organ with a reported low incidence of severe late radiation toxicity of only 1-7% (Haie-Meder et al., 1994; Eifel et al., 1995). However, recent studies have reported a higher incidence of late vaginal toxicity in patients of cervical cancer treated with chemoradiation (Gondi et al., 2012) and radiation induced vaginal changes like vaginal shortening and dyspareunia can have a significant impact on the sexual quality of life in these patients (Bergmark et al., 1999). So far, in a single study by Fidorva et al. (2010) no correlation could be demonstrated between the D2cc DVH parameter and vaginal shortening and telangiectasia in patients with cervical cancer undergoing image guided adaptive brachytherapy (Fidorva et al., 2010). The present study is similar to the study done by Fidorva et al. (2010) where we tried to evaluate the correlation between the DVH parameters with vaginal shortening, telangiectasia and dyspareunia. In addition, we also assessed the quality of sexual life in these patients at one year of completion of treatment.

Materials and Methods

A total of thirty five patients who underwent MRI guided image based brachytherapy from March 2011 to July 2013 were included in the study. For the study, the patients were assessed at one year of completion of treatment.

All the patients underwent external radiotherapy (EBRT) 46Gy in 23 fractions over four and a half weeks with concurrent weekly cisplatin (40mg/m²) and brachytherapy was performed towards the last week of external radiotherapy or at completion of treatment. A total four fractions of 7Gy high dose rate brachytherapy (HDR) were delivered and two applications of brachytherapy were performed one week apart.

Brachytherapy procedure

The intracavitary brachytherapy application was performed under general anesthesia with patient in lithotomy position. The bladder was catheterized and all patients underwent bowel preparation prior to the procedure. An examination under anesthesia was performed to note the extent of residual disease. The brachytherapy procedure was performed under ultrasound guidance. The application was done using MRI compatible ring tandem applicators Nucletron, an Elekta company (Elekta AB, Stockholm, Sweden) with nominal dimensions of 40, 60mm in length for the tandem (diameter 6mm) and 26 and 30mm for the diameter for the ring with 45 and 60 degree curvature. Vaginal packing was done with roller gauze anterior and posterior to the applicator to push the bladder and rectum respectively.

MRI at brachytherapy

After the procedure, the patients underwent an MRI with the applicator in situ for the first application. A CT scan was done thereafter prior to each brachytherapy fraction. A standardized bladder filling was performed before imaging and before each treatment. The bladder was first drained and 50ml of saline was instilled in the bladder via the urinary catheter. The urine was then allowed to drain with gravity to attain a constant bladder filling. MRI imaging was done in accordance with the protocol described by Dimopoulos et al (Dimopoulos et al., 2006). Images were acquired on a 3-Tesla Magnetron Veiro System (Siemens AG, Healthcare Sector, Erlangen, Germany) with pelvic surface coils with patient in supine position. The section thickness was 5mm with no intersection gap. The axial images were obtained from

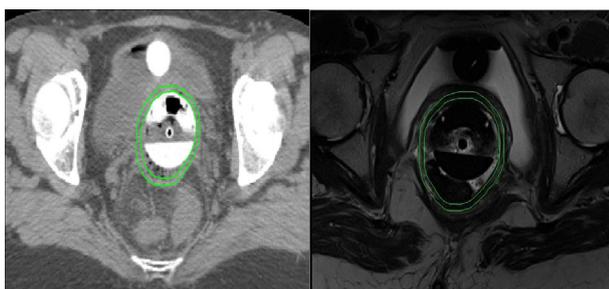


Figure 1. A) Vaginal Contouring on CT; B) Vaginal Contouring on MRI

the level above uterine fundus to the inferior border of symphysis pubis or below in case of vaginal tumor extension. The sagittal images were obtained between the internal obturator muscles. The coronal, para-coronal and para-axial images included the tumour, entire cervix, corpus uteri, parametrium and vagina. For the second application, the CT scan was done without contrast and CT slices were taken at 2.5mm intervals from the level of 3-4cm above the fundus superiorly to the level of ischial tuberosities inferiorly.

Contouring and brachytherapy treatment planning

The MRI images were transferred to Oncentra master plan version 4.3 (Nucletron, an Elekta company). The contouring was done on axial T2 weighted MRI images. The GTV, HRCTV and the OARs were contoured on MRI at brachytherapy in accordance with the GEC-ESTRO guidelines. Applicator reconstruction was done on MRI images with the help of CT image data using rigid registration technique. For the first application, the tandem of the applicator was contoured on both the CT and MR image data sets using the pearl contouring tool of 3 mm diameter sphere. These applicator contours were aligned by rotating and translating the 3D CT and MR images dataset interactively. After verification of the fusion at different important landmark points, digitization for applicator reconstruction on MR image were performed with the help of the spy glass tool along the centre of applicator axis of CT images. The standard dwell positions were used and the dose was initially prescribed to point A. The dwell positions for 6 cm uterine tandem were 3, 6, 9, 12, 15, 18, 21 and 24 and for 3.4cm ring 7, 8, 9, 10, 25, 26, 27 and 28 with a step size of 2.5mm. The doses to the HRCTV and the OAR's were then evaluated and optimization was done keeping point A as the starting reference point. The target dose per fraction for the HRCTV was to achieve D90 dose of minimum 7Gy. The total planned EQD2 for HRCTV was ≥ 85 Gy (alpha/beta=10) and for the 2cc bladder, rectum and sigmoid were limited to ≤ 90 Gy, ≤ 75 Gy and ≤ 75 Gy (alpha/beta=3Gy) respectively.

Contouring of the vagina was done on the MRI and CT scan at each fraction. The vaginal walls were identified by the low signal intensity on MRI and on CT by the relative hypo attenuation from the mucosa (Figure 1). In sections where the vaginal walls could not be discriminated, the thickness of the vaginal wall was assumed to be 4 mm. The D 0.1cc, 1cc, 2cc and 5cc were calculated for each fraction with the help of Oncentra master plan version 4.3 (Nucletron, an Elekta company) planning system. The total cumulative 2Gy equivalent dose (EQD2) including the dose received from EBRT was calculated.

After completion of treatment, the patients were followed up every three months for the first year and every six months thereafter. An MRI was done at 3 months and at one year of completion of treatment. A clinical examination was done at each visit. The length of the vagina was assessed prior to starting treatment and at one year of completion of treatment. The length of the vagina was assessed with the help of a narrow spatula from the posterior fornix up to the introitus that was then measured

with a scale. The vaginal morbidity was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 3. The sexual function was assessed prior to treatment and at one year of completion of treatment and EORTC QOL Cx24 questions 48-53 pertaining to the sexual life were considered (Greimel et al., 2006).

ETHICS

Oral informed consent was obtained from patients for this dosimetric analysis and the study conforms to the ethical guidelines of the “World Medical Association (WMA) Declaration of Helsinki-Ethics Principles for Medical Research Involving Human Subjects” adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, South Korea, October 2008.

Statistical analysis

Statistical analysis was done using the SPSS version 12. Pearson’s correlation coefficient was used to calculate the correlation between the dose and vaginal toxicity. A two-sided test of significance was used. ‘p’ value of less than 0.05 were considered significant.

Table 1. Mean Vaginal Doses with Standard Deviation

DVH	Mean fraction dose with SD (Gy)	Range (Gy)	Mean EQD2 (EBRT+Brachy) with SD (Gy)	Range (Gy)
0.1 cc	22.24±2.8	13.5-28.1	492.4±111.4	282.9-722.9
1cc	14.2±2.3	10.0-18.7	242.5±50.5	145.2-352.6
2cc	10.7±1.4	8.1-12.9	162.9±23.1	122.8-218.7
5cc	6.7±0.8	4.9-9.5	98.0±8.9	83.3-117.8

Table 2. Vaginal Toxicity and Values for Correlation Coefficient with Two-Sided Test of Significance

	EQD				
	0.1cc	1cc	2cc	5cc	10cc
Vaginal shortening					
Correlation coefficient	-0.13	-0.09	-0.03	-0.09	-0.33
Sig (two tailed)	0.45	0.61	0.85	0.62	0.05
Telangectasia					
Correlation coefficient	-0.23	-0.19	-0.1	0.28	0.21
Sig (two tailed)	0.18	0.26	0.56	0.11	0.21
Dysparunia					
Correlation coefficient	0.16	0.26	0.06	0.17	-0.1
Sig (two tailed)	0.35	0.13	0.73	0.38	0.55

Table 3. Assessment of Sexual Function-Quality of Sexual Life (EORTC Cx24; Questions 19-24)

No. of Patients	Four weeks	At One year
	Prior to treatment	follow up
Total patients sexually Active	4	13
Sexually inactive due to fear of pain	7	7
Fear of pain but active	2	8
Vaginal tightness	0	4
Vaginal shortness	0	3
Dysparunia	1 (grade 3)	8 (grade3-1)
Overall sexual enjoyment		
Not at all (Gd-1)	1	2
A little (Gd-2)	1	4
Quite a bit (Gd-3)	2	5
Very Much (Gd-4)	0	2

Results

Thirty-five patients were evaluated at one year of treatment completion. The mean age of patients was 48.2 years (range 28-72 years). The stage of the disease was as follows: Ib2-2; IIa-1; IIb-30, IIIb-2. In eleven patients, there was extension of disease to the vagina. The maximum extension into the vagina was 2cm. Vaginal shortening as observed in 22 out of 30 (62.8%) patients of which 12 (34.2%) patients had grade-1, 9(25.7%) patients had grade-2 and only 1(2.8%) had grade-3 vaginal shortening. Nine (25.7%) had grade-1 vaginal dryness and none of the patients had grade-2 or 3 vaginal dryness. In 10 (28.5%) patients, there was contact bleeding.

The calculated mean vaginal doses with one standard deviation (SD) for single fraction of prescribed dose of 7Gy were D0.1cc-22.24±2.87Gy; D1cc-14.23±2.35Gy; D2cc-10.77±1.17Gy and D5cc-6.73±0.81Gy. The total 2Gy equivalent dose (EQD2) including external beam radiotherapy and four fractions of brachytherapy was as follows: D0.1cc-492.39±111.43Gy; D1cc-242.48±50.51Gy; D2cc-162.96±23.13Gy and D5cc-90.02±8.89Gy (Table 1).

On assessment of the sexual function 29/35, patients

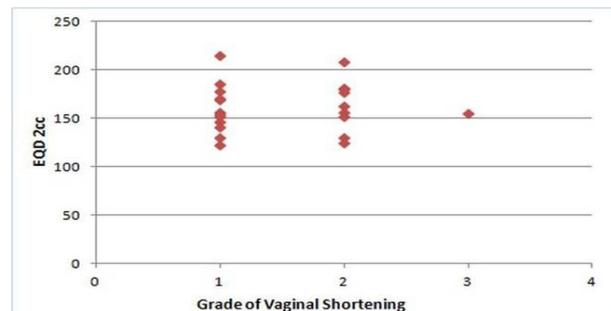


Figure 2. Dose 2cc Volume for Vaginal Shortening

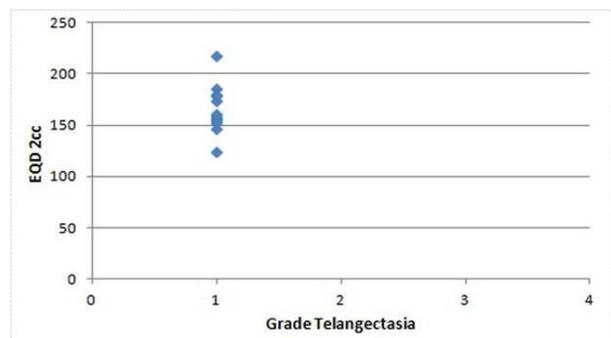


Figure 3. Dose 2cc Volume for Vaginal Telangectasia

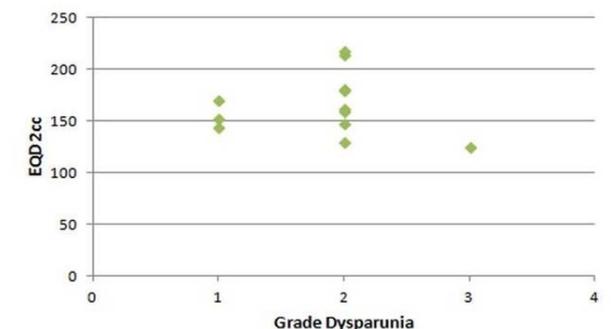


Figure 4. Dose 2cc Volume for Dysparunia

were sexually active prior to diagnosis of cervical cancer, 4/35 (11.4%) patients were sexually active after diagnosis but prior to radiotherapy. By one year of treatment, 13/35 (37.1%) patients had resumed sexual activity. Dysparunia was the most common side effect reported by the patients. Eight out of 13 patients complained of dysparunia at one year compared to only one patient before the start of treatment. Only one patient had grade 3 dysparunia both prior to starting and at one year follow up. Of the sexually active patients, four patients complained of vaginal tightness, three patients complained of vaginal shortening at follow up (Table 2), and on assessment, all these patients had grade 1 vaginal shortening. All the patients with vaginal tightness and shortening complained of mild dysparunia that did not seem to effect the overall sexual enjoyment. Vaginal shortening was more common in patients who were sexually inactive and majority had grade 2-3 vaginal shortening. No correlation could be demonstrated between the D0.1cc, D1cc, D2cc and D5cc for vaginal shortening, telangectasia and dysparunia (Table 2, Figure 2, 3, 4).

Discussion

External radiotherapy with concurrent Cisplatin followed by brachytherapy is the standard treatment for patients with locally advanced cervical cancer (Zhao et al., 2012). Although excellent local controls can be achieved with the use of radiotherapy (Peseet al., 2012), a few patients may have significant radiation induced toxicities. The most commonly reported toxicities are the radiation cystitis and proctitis (Yang et al., 2012) and vaginal toxicities are seldom reported. In the treatment of cervical cancer, the vagina receives very high doses due to its close proximity to the radiation sources. Though not very often reported, radiation induced vaginal changes are very common but often overlooked. Although the reported incidence of grade 3 and 4 toxicity is low (Haie-Meder et al., 1994; Eifel et al., 1995; Au et al., 2003), even grade 1-2 vaginal toxicity can have a devastating effect on the patient's sexual life and the overall quality of life. In the present study, no correlation could be established between the dose volume parameters and the vaginal toxicity. The results are in concurrence with study reported by Fidorva et al where 37 patients treated with definitive radiotherapy and MRI guided brachytherapy were assessed for radiation induced vaginal side effects (Fidorva et al., 2010). The mean dose reported (D2cc) to the upper vagina which receives very high doses was 141Gy EQD2 and no correlation could be demonstrated between D2cc dose volume parameter and the vaginal toxicity. The lack of correlation in both the studies can be due to difficulty in assessing the dose to the vagina as high inaccuracies in contouring and geometric positioning that have been reported using both point dose values and DVH parameters for the vaginal wall. Contouring of the vaginal wall is difficult as it is thin and accurate delineation is limited with the present treatment planning systems (Berger et al., 2007). Hence, true estimation of vaginal doses is challenging. Since, it is not necessary that toxicity may be related only to the high dose regions, it is also important

to study the dose effect in the lower dose regions also (Fidorva et al., 2007).

Westerveld et al. (2013) in a recent study suggested 2-D vaginal points for comprehensive reporting of vaginal points for use as a surrogate for evaluation of spatial dose distribution in the upper, middle and lower vagina. Large dose variations were observed between varying dose contributions from both external radiotherapy and brachytherapy. However, correlation of vaginal toxicity using these vaginal points needs to be studied (Westerveld et al., 2013).

In our study, additionally we tried to assess the quality of sexual life in our patients. After one year of treatment, only 13 patients were sexually active and grade 1 dysparunia was the most commonly reported sexually related problem. Lammerink et al reviewed the sexual functioning in patients treated for cervical cancer. Of the twenty studies reviewed, dysparunia, lack of lubrication and a decreased sexual interest were more frequent in cervical cancer survivors compared to the healthy controls (Lammerink et al., 2012). Although no difference was found between cervical cancer survivors treated with surgery and controls, cervical cancer survivors treated with radiotherapy had more dysparunia as compared to controls (Frumowitz et al., 2005). In a study by Nout et al, quality of life quality of life was compared for patients with endometrial cancer treated with external radiotherapy versus vaginal brachytherapy. Sexual activity and interest were found to be lowest (15%) at baseline i.e post surgery. This increased to 39% after six months of surgery. A similar observation was made in our study also and prior to treatment only 11.4% patients were sexually active which increased to 37.1% at one year after treatment completion (Nout et al., 2009).

Jenson et al. (2004) studied the sexual and vaginal changes in patients with cervical cancer treated with radiotherapy and the sexual changes in patients with cervical cancer treated with radical hysterectomy. In patients treated with surgery dysparunia was more pronounced during the first three months after surgery whereas in patients treated with radiotherapy, dysparunia occurred more in the first two years compared to controls (Jensen et al., 2004).

The other sexual related problem reported in our study was vaginal shortness and tightness that was more common and severe in patients who were sexually inactive. Although patients who were sexually active reported a fewer incidence of vaginal shortening, mild dysparunia was reported by a significant number of these patients. Nout et al compared the five-year quality of life for endometrial cancer patients treated with pelvic radiotherapy and vaginal brachytherapy with the norm data. An increased grade 1-2 mucosal atrophy was reported at 3 years which affected the sexual functioning and increased sexual symptoms were observed in patients compared to the age matched norm data (Nout et al., 2012).

Regular vaginal dilatation has recommended by many centers in order to reduce the incidence of vaginal shortening. However, in the present study, vaginal dilators were not used as this practice is not routinely followed at our center. Miles et al reviewed the benefits and harms of

using a vaginal dilation therapy in patients who received pelvic radiotherapy. The authors concluded that there was no reliable evidence to suggest that routine dilatation prevented vaginal toxicity of improved the quality of life (Miles et al., 2010).

Studies have shown that patient reported side effects, especially the sexual dysfunction occur more commonly than that reported in literature (Grover, 2012). The reason why sexual toxicity has been frequently under reported is due to patient reluctance as a result of which these problems are infrequently expressed. Since studies have shown that symptomatic vaginal toxicities can adversely affect the patient's quality of life (Nout et al., 2009), it is important for the clinicians to discuss these issues with the patients and include them in the toxicity grading scale (Bahng et al., 2012).

The drawback of our study is the limited sample size and outcome reporting from a single institution. Also quality of sexual of life may depend on a majority of factors including the patient age, social and psychological issues which were not addressed and are beyond the scope of this study. In the present study, no correlation could be demonstrated between the radiation dose, vaginal toxicity and its effect of the sexual quality of life. This study highlights the need for methods to accurately define the vaginal dose distributions in order to evaluate the correlation with vaginal morbidity. On the other hand, effective communication and counseling pertaining to the sexual function is required in patients treated for gynecological cancers. Focus and attempt to improve quality of sexual life is required in these patients

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